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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PARAS JR, PETER	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,621	CHU ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *26-39,50-59 and 64-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,40-49 and 60-63* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-25, 40-49, and 60-63 in Paper No. 8 is acknowledged.

Claims 26-39, 50-59, and 64-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Applicant's preliminary amendment received on 11/21/02 has been entered. Claim 10 has been amended.

Claim Objections

Claim 1 is objected to because of the following informalities: the claim, in line 1 recites the article "a" consecutively. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2 and 9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-2 and 9 are directed to a transgenic animal the scope of which encompasses a human being. A human being is non-statutory subject matter. As such,

the recitation of the limitation "non-human" would be remedial for claim 10. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25, 40-49, and 60-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption of the endogenous GPX1 gene and a homozygous disruption of the endogenous GPX2 gene, wherein no functional GPX1 and GPX 2 are produced, and wherein said mouse exhibits a phenotype of ileitis, colitis, decreased rate of weight gain, hypothermia, perianal ulceration, diarrhea, wasting syndrome, inflammatory bowel disease, dysplasia in the small bowel, and tumors in the small bowel, does not reasonably provide enablement for the other transgenic animals encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic mouse whose genome comprises a homozygous disruption of the endogenous GPX1 gene and a homozygous disruption of the endogenous GPX2 gene.

The specification teaches the generation of transgenic mice comprising a homozygous disruption of the endogenous GPX1 gene and a homozygous disruption of the endogenous GPX2 gene, wherein no functional GPX1 and GPX 2 are produced. See the working examples beginning on page 22. The specification teaches that these homozygous, double knockout mice exhibit a phenotype of ileitis, colitis, decreased rate of weight gain, hypothermia, perianal ulceration, diarrhea, wasting syndrome, inflammatory bowel disease, dysplasia in the small bowel, and tumors in the small bowel. While the specification has taught the generation of such homozygous double, knockout mice having a phenotype of ileitis, colitis, decreased rate of weight gain, hypothermia, perianal ulceration, diarrhea, wasting syndrome, inflammatory bowel disease, dysplasia in the small bowel, and tumors in the small bowel, the specification has not taught the generation of the other transgenic animals encompassed by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support the creation of other transgenic non-human animals encompassed by the claims. See pages 22-34 of the specification.

As a first issue, the following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 1-2, 9 and 16 as they read on embryonic stem cells and transgenic knockout non-human animals.

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest.

Presently, the transgenic knockout technology is limited to the mouse system. With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a homozygous disruption of the endogenous GPX1 gene and a homozygous disruption of the endogenous GPX2 gene other than a transgenic mouse. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are directed to transgenic non-human animals and cells derived therefrom (claims 1-2 and 9) or a method that requires the use of a transgenic non-human animal (claim 16), the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse.

As a second issue, the rejection of claims 1-25, 40-49, and 60-63 is directed to the phenotype associated with the homozygous disruption of GPX1 and GPX2 in a transgenic animal. The specification has provided working examples that exemplify a transgenic mouse genome whose genome comprises a homozygous disruption of the endogenous GPX1 gene and a homozygous disruption of the endogenous GPX2 gene, wherein no functional GPX1 and GPX 2 are produced, which exhibits a phenotype of ileitis, colitis, decreased rate of weight gain, hypothermia, perianal ulceration, diarrhea, wasting syndrome, inflammatory bowel disease, dysplasia in the small bowel, and tumors in the small bowel. The breadth of the claims, as they are directed to broader phenotypes (such as development of cancer as recited in claim 1; one or more signs or symptoms associated with cancer as recited in claims 9 and 16; ileal cancer and myeloleukemia as recited in claims 8, 11, 13, 18, 20; and cancer of the lower gastro-intestinal tract as recited in claim 41), is not supported by the teachings and working examples provided by the instant specification. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). Given the lack of guidance provided by the specification with regard to the other phenotypes encompassed by the claims, it

would be difficult to predict any phenotype resulting from disruption of the both the endogenous GPX1 and GPX2 genes in a transgenic animal, particularly a mouse.

Moreover, the specification has disclosed specific phenotypes exhibited by the homozygous double knockout mouse; it does not appear that mice, which are heterozygous for a disruption in either GPX1 or GPX2 exhibit a phenotype. However, claims 40 and 60-63, as written, do not include a phenotype that differs from the wild-type mouse. The skilled artisan would know how to use a transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the exemplified transgenic mice that have the phenotypes disclosed in the specification may be used for drug testing according to the instant specification. The specification overcomes the unpredictability in obtaining a phenotype associated with a disruption of the disruption of the both the endogenous GPX1 and GPX2 genes; however, the claims are not commensurate in scope with the enabled phenotype disclosed in the specification. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic knockout animal that lacks a phenotype.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is directed to a transgenic mouse whose genome comprises a homozygous disruption of both the endogenous Gpx1 gene and Gpx2 genes. The specification has defined a transgenic mouse comprising a homozygous disruption in the endogenous Gpx1 gene and the endogenous Gpx 2 gene. The specification has not defined a transgenic mouse whose genome comprises a disruption in more than one Gpx2 gene as recited in the claims. It appears that the language of claim 1, reciting Gpx2 genes is an inadvertent typographical error. Correction is required. Claims 2-8 depend from claim 1.

Claim 19 is unclear as written. The claim is directed to the model of claim 18, however, claim 18 is directed to a method and not a model. As such it is not clear if claim 19 is directed to a method or a model. It appears that the language of claim 19 is an inadvertent typographical error. Correction is required.

Drawings

New corrected drawings are required in this application because figure 5 contains handwritten alterations. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to

the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.
Art Unit 1632

PETER PARAS
PATENT EXAMINER